



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<p><b>(21) International Application Number:</b> PCT/US97/05979</p> <p><b>(22) International Filing Date:</b> 10 April 1997 (10.04.97)</p> <p><b>(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application</b>          US 08/542,854 (CIP)          Filed on 13 October 1995 (13.10.95)</p> <p><b>(71) Applicant (for all designated States except US):</b> NEUROGEN CORPORATION [US/US]; 35 N.E. Industrial Road, Branford, CT 06405 (US).</p> <p><b>(72) Inventors; and</b>  <b>(75) Inventors/Applicants (for US only):</b> HORVATH, Raymond, F. [CA/US]; 239B Twin Lakes Road, North Branford, CT 06471 (US). HUTCHINSON, Alan [US/US]; 175 Bartlett Drive, Madison, CT 06443 (US).</p> <p><b>(74) Agent:</b> SARUSSI, Steven, J.; McDonnell Boehnen Hulbert &amp; Berghoff, 300 South Wacker Drive, Chicago, IL 60606 (US).</p>		<p><b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b>  <i>With international search report.</i></p>
<b>(54) Title:</b> CERTAIN PYRROLOPYRIDINE DERIVATIVES; NOVEL CRF1 SPECIFIC LIGANDS		
<p><b>(57) Abstract</b></p> <p>Disclosed are compounds of formula (I) wherein Ar is optionally substituted aryl or heteroaryl; R<sub>1</sub> is hydrogen or alkyl; R<sub>7</sub> is hydrogen or alkyl; R<sub>2</sub> is hydrogen, halogen, alkyl or alkoxy; or R<sub>1</sub> and R<sub>2</sub> taken together with the ring to which they are attached for a 5-9 membered saturated or aromatic ring optionally having a hetero atom selected from oxygen, sulfur or nitrogen; R<sub>3</sub> and R<sub>4</sub> are independently hydrogen, alkyl, cycloalkyl, aryl or heteroaryl groups; or R<sub>3</sub> and R<sub>4</sub> together with the nitrogen atom to which they are attached form a 5-8 membered ring; and R<sub>5</sub> is hydrogen, halogen, straight or branched chain lower alkyl having 1-6 carbon atoms, or straight or branched chain lower alkoxy or thioalkoxy having 1-6 carbon atoms, which compounds are highly selective partial agonists or antagonists at human Corticotropin-Releasing Factor 1 (CRF1) receptors and are useful in the diagnosis and treatment of treating stress related disorders such as post traumatic stress disorder (PTSD) as well as depression, headache and anxiety.</p>		

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**Certain Pyrrolopyridine Derivatives;  
Novel CRF1 Specific Ligands**

5

**BACKGROUND OF THE INVENTION**

**Field of the Invention**

10        This invention relates to certain substituted pyrrolopyridine derivatives which selectively bind to Corticotropin-Releasing Factor (CRF) receptors. More specifically, it relates to tetrahydro-5H-pyrido[2,3-b]indol-4-amines, 9H-pyrido[2,3-b]indol-4-amines, and 1H-pyrrolo[2,3-]pyridin-4-amines, and their use as antagonists of Corticotropin-Releasing Factor in the treatment of various disease states.

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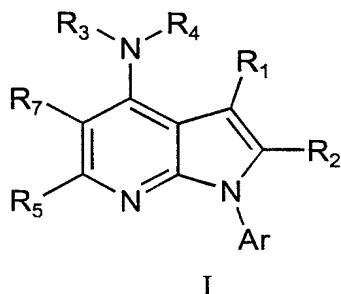
**Description of the Related Art**

      Corticotropin-releasing factor (CRF) antagonists are mentioned in U.S. patents 4,605,642 and 5,063,245 referring to peptides and pyrazoline derivatives, respectively. The importance of CRF antagonists is described in the literature, for example, as discussed in U.S. Patent No. 5,063, 245, which is incorporated herein by reference in its entirety. CRF antagonists are considered effective in the treatment of a wide range of diseases including stress-related illnesses, such as stress-induced depression, anxiety, and headache. Other diseases considered treatable with CRF antagonists are discussed in U.S. Patent No. 5,063,245 and Pharm. Rev., 43: 425-473 (1991).

25        International Application discloses pyrrolo[2,3-d]pyrimidines as having Corticotropin-Releasing Factor antagonist activity. J. Het. Chem. 9, 1077 (1972) describes the synthesis of 9-phenyl-pyrrolo[3,2-d] pyrimidines.

**SUMMARY OF THE INVENTION**

This invention provides novel compounds of Formula I which interact with CRF receptors. Further, the invention provides pharmaceutical compositions comprising compounds of Formula I. It further relates to the use of such compounds in treating stress related disorders such as post traumatic stress disorder (PTSD) as well as depression, headache and anxiety. Accordingly, a broad embodiment of the invention is directed to a compound of Formula I:



wherein

Ar is optionally substituted aryl or heteroaryl;

R<sub>1</sub> is hydrogen or alkyl;

R<sub>7</sub> is hydrogen or alkyl;

R<sub>2</sub> is hydrogen, halogen, alkyl or alkoxy; or

R<sub>1</sub> and R<sub>2</sub> taken together with the ring to which they are attached for a 5-9 membered saturated or aromatic ring optionally having a hetero atom selected from oxygen, sulfur or nitrogen;

R<sub>3</sub> and R<sub>4</sub> are independently hydrogen, alkyl, cycloalkyl, aryl or heteroaryl groups; or

R<sub>3</sub> and R<sub>4</sub> together with the nitrogen atom to which they are attached form a 5-8 membered ring; and

R<sub>5</sub> is hydrogen, halogen, straight or branched chain lower alkyl having 1-6 carbon atoms, or straight or branched chain lower alkoxy or thioalkoxy having 1-6 carbon atoms.

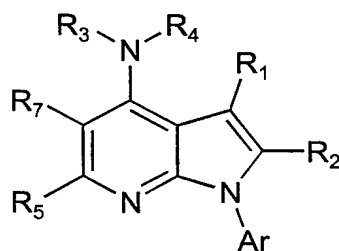
The compounds of the invention are highly selective partial agonists or antagonists at CRF receptors and are useful in the diagnosis and treatment of stress related disorders such as post traumatic stress disorder (PTSD) as well as depression and anxiety.

Thus, the invention provides compounds, including pharmaceutically acceptable salts of the compounds of formula I, and pharmaceutical compositions for use in treating disease states associated with Corticotropin-Releasing Factor. The invention further provides

methods including animal models relevant to the evaluation of the interaction of the compounds of the invention with CRF receptors. This interaction results in the pharmacological activities of these compounds.

### **DETAILED DESCRIPTION OF THE INVENTION**

- 5 In addition to the novel compounds of the instant invention described by general formula I above, the invention encompasses compounds of formula IA:



IA

- 10 wherein

Ar is phenyl, 2-, 3-, or 4-pyridyl, 2-or 3-thienyl, 4-or 5-pyrimidinyl, each of which is monosubstituted, or optionally di- or trisubstituted with halogen, hydroxy, lower alkyl, or lower alkoxy, provided that at least one of the ortho positions of Ar is substituted;

R<sub>1</sub> is hydrogen or lower alkyl;

- 15 R<sub>7</sub> is hydrogen or alkyl;

R<sub>2</sub> is hydrogen, halogen, lower alkyl, lower alkoxy, or thioalkoxy; or

R<sub>1</sub> and R<sub>2</sub> taken together represent -(CH<sub>2</sub>)<sub>n</sub>-A-(CH<sub>2</sub>)<sub>m</sub>- where n is 2, 3 or 4, A is methylene, oxygen, sulfur or NR<sub>6</sub>, wherein R<sub>6</sub> is hydrogen or lower alkyl, and m is 0, 1 or 2; or

R<sub>1</sub> and R<sub>2</sub> taken together represent -CH=A=CH=CH-, where A is CH or N;

- 20 R<sub>3</sub> and R<sub>4</sub> are not both hydrogen and independently represent

hydrogen, lower alkyl, phenyl, 2-, 3-, or 4-pyridyl, 2-or 3-thienyl or 2-, 4-, or 5-pyrimidinyl, each of which is optionally mono- or disubstituted with halogen, hydroxy, lower alkyl, or lower alkoxy,

phenylalkyl, 2-, 3-, or 4-pyridylalkyl, 2-or 3-thienylalkyl, or 2-, 4-, or 5-pyrimidinylalkyl, where each alkyl is lower alkyl,

- 25 cycloalkyl having 3-8 carbon atoms, cycloalkyl lower alkyl, 2-hydroxyethyl or 3-hydroxypropyl, each of which is optionally mono or disubstituted with lower alkyl; or

R<sub>3</sub> and R<sub>4</sub> taken together represent -(CH<sub>2</sub>)<sub>n</sub>-A-(CH<sub>2</sub>)<sub>m</sub>-

where n is 2, 3 or 4,

m is 1, 2, or 3; and

G is methylene, 1,2 phenylene, oxygen, sulfur or NR<sub>6</sub>,

wherein R<sub>6</sub> is lower alkyl, phenyl, 2-, 3-, or 4-pyridyl, 2- or 3-thienyl or 2-, 4-

or 5-pyrimidinyl, or

R<sub>6</sub> is phenylalkyl, 2-, 3-, or 4-pyridylalkyl, 2- or 3-thienylalkyl, or 2-, 4- or 5-pyrimidinylalkyl where each alkyl is lower alkyl; and

R<sub>5</sub> is hydrogen, halogen, lower alkyl, lower alkoxy, or thioalkoxy.

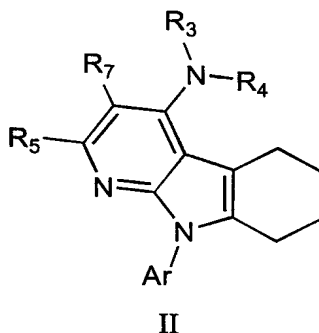
Preferred compounds of formula I are those where Ar is a disubstituted aryl or heteroaryl group having substituents in one ortho position and the para position. More preferred compounds of formula I are those where Ar is a trisubstituted aryl or heteroaryl group having substituents in both ortho positions and the para position, i.e., a 2, 4, 6-trisubstituted aryl group. The most preferred aryl group is phenyl. The preferred aryl substituents are lower alkyl groups or halogen, particularly fluorine. More preferred aryl substituents are methyl groups.

Other preferred compounds of formula I are those where the NR<sub>3</sub>R<sub>4</sub> group is a disubstituted amino group, e.g., dialkyl amino. A particularly preferred NR<sub>3</sub>R<sub>4</sub> group is dipropylamino.

In compounds of formula I, R<sub>5</sub> is preferably lower alkyl and, more preferably, methyl; and R<sub>7</sub> is preferably hydrogen.

In still other preferred compounds of formula I, R<sub>1</sub> and R<sub>2</sub> taken together represent - (CH<sub>2</sub>)<sub>n</sub>-A-(CH<sub>2</sub>)<sub>m</sub>- where n is 2, 3 or 4, A is methylene, oxygen, sulfur or NMe, and m is 0, 1, or 2.

The invention further provides compounds of formula II



wherein

Ar is phenyl, 2-, 3-, or 4-pyridyl, 2- or 3-thienyl, 4- or 5-pyrimidinyl, each of which is monnosubstituted or optionally di- or trisubstituted with halogen, hydroxy, lower alkyl, or lower alkoxy, provided that at least one of the ortho positions of Ar is substituted;

R<sub>7</sub> is hydrogen or alkyl;

R<sub>3</sub> and R<sub>4</sub> are not both hydrogen and independently represent

hydrogen, lower alkyl, phenyl, 2-, 3-, 4-pyridyl, 2- or 3-thienyl or 2-, 4-, or 5-pyrimidinyl, each of which is optionally mono- or disubstituted with halogen, hydroxy, lower alkyl, or lower alkoxy;

phenylalkyl, 2-, 3-, or 4-pyridylalkyl, 2- or 3-thienylalkyl, or 2-, 4-, or 5-pyrimidinylalkyl, where each alkyl is lower alkyl,

cycloalkyl having 3-8 carbon atoms, cycloalkyl lower alkyl, 2-hydroxyethyl or 3-hydroxypropyl, each of which is optionally mono or disubstituted with lower alkyl; or

R<sub>3</sub> and R<sub>4</sub> taken together represent  $-(CH_2)_n-G-(CH_2)_m-$

where n is 2, or 3;

m is 1, 2, or 3;

G is methylene, 1,2 phenylene, oxygen, sulfur or NR<sub>6</sub>,

wherein R<sub>6</sub> is lower alkyl, phenyl, 2-, 3-, or 4-pyridyl, 2- or 3-thienyl or 2-, 4- or 5-pyrimidinyl, or

R<sub>6</sub> is phenylalkyl, 2-, 3-, or 4-pyridylalkyl, 2- or 3-thienylalkyl, or 2-, 4- or 5-pyrimidinylalkyl, where each alkyl is lower alkyl; and

R<sub>5</sub> is hydrogen, halogen, lower alkyl, lower alkoxy, or thioalkoxy.

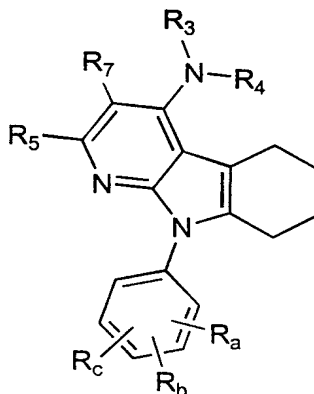
Preferred compounds of formula II are those where Ar is a disubstituted aryl or heteroaryl group having substituents in one ortho position and the para position. More preferred compounds of formula I are those where Ar is a trisubstituted aryl or heteroaryl group having substituents in both ortho positions and the para position, i.e., a 2, 4, 6-trisubstituted aryl group. The most preferred aryl group is phenyl. The preferred aryl substituents are lower alkyl groups or halogen, particularly fluorine. More preferred aryl substituents are methyl groups.

Other preferred compounds of formula II are those where the  $\text{NR}_3\text{R}_4$  group is a disubstituted amino group, e.g., dialkyl amino. A particularly preferred  $\text{NR}_3\text{R}_4$  group is dipropylamino.

In yet other preferred compounds of formula II,  $\text{R}_7$  is hydrogen.

5

The invention further provides compounds of formula III



III

wherein

10  $\text{R}_a$ ,  $\text{R}_b$ , and  $\text{R}_c$  independently represent halogen, hydroxy, lower alkyl, or lower alkoxy;  
 $\text{R}_7$  is hydrogen or alkyl;

$\text{R}_3$  and  $\text{R}_4$  are independently represent

hydrogen, lower alkyl, phenyl, 2-, 3-, 4-pyridyl, 2- or 3-thienyl or 2-, 4-, or 5-  
 15 pyrimidinyl, each of which is optionally mono- or disubstituted with  
 halogen, hydroxy, lower alkyl, or lower alkoxy;

phenylalkyl, 2-, 3-, or 4-pyridylalkyl, 2-or 3-thienylalkyl, or 2-, 4-, or 5-  
 pyrimidinylalkyl, where each alkyl is lower alkyl,

cycloalkyl having 3-8 carbon atoms, cycloalkyl lower alkyl, 2-hydroxyethyl or  
 3-hydroxypropyl, each of which is optionally mono or disubstituted  
 20 with lower alkyl; or

$\text{R}_3$  and  $\text{R}_4$  taken together represent  $-(\text{CH}_2)_n-\text{G}-(\text{CH}_2)_m-$

where n is 2, or 3;

m is 1, 2, or 3; and

G is methylene, 1,2 phenylene, oxygen, sulfur or  $\text{NR}_6$ ,

25 wherein  $\text{R}_6$  is lower alkyl, phenyl, 2-, 3-, or 4-pyridyl, 2- or 3-thienyl  
 or 2-, 4- or 5-pyrimidinyl, or



$R_6$  is phenylalkyl, 2-, 3-, or 4-pyridylalkyl, 2- or 3-thienylalkyl, or 2-, 4- or 5-pyrimidinylalkyl, where each alkyl is lower alkyl; and

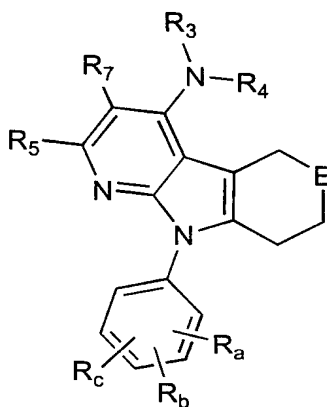
$R_5$  is hydrogen, halogen, lower alkyl, lower alkoxy, or thioalkoxy.

Preferred compounds of formula III are those where at least one of  $R_a$ ,  $R_b$ , or  $R_c$  is present in one of the two ortho positions of the phenyl group to which they are attached. More preferred compounds of formula III are those where at least two of  $R_a$ ,  $R_b$ , or  $R_c$  are present in one ortho position and the para position. Still more preferred compounds of formula III are those where the  $R_a$ ,  $R_b$ , or  $R_c$  are present in both ortho positions and the para position, i.e., a 2, 4, 6-trisubstituted phenyl group. The preferred  $R_a$ ,  $R_b$ , or  $R_c$  are lower alkyl groups or halogen, particularly fluorine. More preferred aryl substituents are methyl groups.

Other preferred compounds of formula III are those where the  $NR_3R_4$  group is a disubstituted amino group, e.g., dialkyl amino. A particularly preferred  $NR_3R_4$  group is dipropylamino.

In still other preferred compounds of formula III,  $R_7$  is hydrogen.

The invention further provides compounds of formula IV



IV

wherein

E represents  $CH_2$  or  $NR_6$ , wherein  $R_6$  is hydrogen or lower alkyl;

$R_7$  is hydrogen or alkyl;

$R_a$ ,  $R_b$ , and  $R_c$  independently represent halogen, hydroxy, lower alkyl, or lower alkoxy;

$R_3$  and  $R_4$  independently represent

hydrogen, lower alkyl, phenyl, 2-, 3-, 4-pyridyl, 2- or 3-thienyl or 2-, 4-, or 5-pyrimidinyl, each of which is optionally mono- or disubstituted with halogen, hydroxy, lower alkyl, or lower alkoxy;

phenylalkyl, 2-, 3-, or 4-pyridylalkyl, 2- or 3-thienylalkyl, or 2-, 4-, or 5-pyrimidinylalkyl, where each alkyl is lower alkyl, cycloalkyl having 3-8 carbon atoms, cycloalkyl lower alkyl, 2-hydroxyethyl or 3-hydroxypropyl, each of which is optionally mono or disubstituted with lower alkyl; or

$R_3$  and  $R_4$  taken together represent  $-(CH_2)_n-G-(CH_2)_m-$

where  $n$  is 2, or 3;

$m$  is 1, 2, or 3; and

$G$  is methylene, 1,2 phenylene, oxygen, sulfur or  $NR_6$ ,

wherein  $R_6$  is lower alkyl, phenyl, 2-, 3-, or 4-pyridyl, 2- or 3-thienyl or 2-, 4- or 5-pyrimidinyl, or

$R_6$  is phenylalkyl, 2-, 3-, or 4-pyridylalkyl, 2- or 3-thienylalkyl, or 2-, 4- or 5-pyrimidinylalkyl, where each alkyl is lower alkyl; and

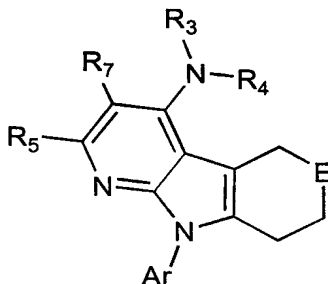
$R_5$  is hydrogen, halogen, lower alkyl, lower alkoxy, or thioalkoxy.

Preferred compounds of formula IV are those where at least one of  $R_a$ ,  $R_b$ , or  $R_c$  is present in one of the two ortho positions of the phenyl group to which they are attached. More preferred compounds of formula IV are those where at least two of  $R_a$ ,  $R_b$ , or  $R_c$  are present in one ortho position and the para position. Still more preferred compounds of formula IV are those where the  $R_a$ ,  $R_b$ , or  $R_c$  are present in both ortho positions and the para position, i.e., a 2, 4, 6-trisubstituted phenyl group. The preferred  $R_a$ ,  $R_b$ , or  $R_c$  are lower alkyl groups or halogen, particularly fluorine. More preferred aryl substituents are methyl groups.

Other preferred compounds of formula IV are those where the  $NR_3R_4$  group is a disubstituted amino group, e.g., dialkyl amino. A particularly preferred  $NR_3R_4$  group is dipropylamino. In preferred compounds of formula IV,  $E$  represents carbon.

In other preferred compounds of formula IV,  $R_7$  is hydrogen.

The invention further provides compounds of formula V



## V

wherein

E represents  $\text{CH}_2$  or  $\text{NR}_6$ , wherein  $\text{R}_6$  is hydrogen or lower alkyl;

$\text{R}_7$  is hydrogen or alkyl;

5 Ar is phenyl, 2-, 3-, or 4-pyridyl, 2- or 3-thienyl, 4- or 5-pyrimidinyl, each of which is monnosubstituted or optionally di- or trisubstituted with halogen, hydroxy, lower alkyl, or lower alkoxy, provided that at least one of the ortho positions of Ar is substituted;

$\text{R}_3$  and  $\text{R}_4$  independently represent

10 hydrogen, lower alkyl, phenyl, 2-, 3-, 4-pyridyl, 2- or 3-thienyl or 2-, 4-, or 5-pyrimidinyl, each of which is optionally mono- or disubstituted with halogen, hydroxy, lower alkyl, or lower alkoxy;  
phenylalkyl, 2-, 3-, or 4-pyridylalkyl, 2- or 3-thienylalkyl, or 2-, 4-, or 5-pyrimidinylalkyl, where each alkyl is lower alkyl,  
15 cycloalkyl having 3-8 carbon atoms, cycloalkyl lower alkyl, 2-hydroxyethyl or 3-hydroxypropyl, each of which is optionally mono or disubstituted with lower alkyl; or

$\text{R}_3$  and  $\text{R}_4$  taken together represent  $-(\text{CH}_2)_n-\text{G}-(\text{CH}_2)_m-$

where n is 2, or 3;

20 m is 1, 2, or 3; and

G is methylene, 1,2 phenylene, oxygen, sulfur or  $\text{NR}_6$ ,

wherein  $\text{R}_6$  is lower alkyl, phenyl, 2-, 3-, or 4-pyridyl, 2- or 3-thienyl or 2-, 4- or 5-pyrimidinyl, or

25  $\text{R}_6$  is phenylalkyl, 2-, 3-, or 4-pyridylalkyl, 2- or 3-thienylalkyl, or 2-, 4- or 5-pyrimidinylalkyl, where each alkyl is lower alkyl; and

$\text{R}_5$  is hydrogen, halogen, lower alkyl, lower alkoxy, or thioalkoxy.

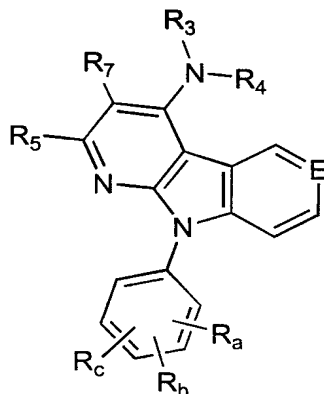
Preferred compounds of formula V are those where Ar is a disubstituted aryl or heteroaryl group having substituents in one ortho position and the para position. More preferred compounds of formula V are those where Ar is a trisubstituted aryl or heteroaryl  
30 group having substituents in both ortho positions and the para position, i.e., a 2, 4, 6-trisubstituted aryl group. The most preferred aryl group is phenyl. The preferred aryl substituents are lower alkyl groups or halogen, particularly fluorine. More preferred aryl substituents are methyl groups.

Other preferred compounds of formula V are those where the  $\text{NR}_3\text{R}_4$  group is a disubstituted amino group, e.g., dialkyl amino. A particularly preferred  $\text{NR}_3\text{R}_4$  group is dipropylamino. In preferred compounds of formula IV, E represents carbon.

Yet other preferred compounds of formula V are those where  $\text{R}_7$  is hydrogen.

5

The invention further provides compounds of formula VI



VI

wherein

- 10 E represents  $\text{CH}_2$  or  $\text{NR}_6$ , wherein  $\text{R}_6$  is hydrogen or lower alkyl;  
 $\text{R}_7$  is hydrogen or alkyl;  
 $\text{R}_a$ ,  $\text{R}_b$ , and  $\text{R}_c$  independently represent halogen, hydroxy, lower alkyl, or lower alkoxy;  
 $\text{R}_3$  and  $\text{R}_4$  independently represent  
 15 hydrogen, lower alkyl, phenyl, 2-, 3-, 4-pyridyl, 2- or 3-thienyl or 2-, 4-, or 5-pyrimidinyl, each of which is optionally mono- or disubstituted with halogen, hydroxy, lower alkyl, or lower alkoxy;  
 phenylalkyl, 2-, 3-, or 4-pyridylalkyl, 2- or 3-thienylalkyl, or 2-, 4-, or 5-pyrimidinylalkyl, where each alkyl is lower alkyl,  
 cycloalkyl having 3-8 carbon atoms, cycloalkyl lower alkyl, 2-hydroxyethyl or  
 20 3-hydroxypropyl, each of which is optionally mono or disubstituted with lower alkyl; or  
 $\text{R}_3$  and  $\text{R}_4$  taken together represent  $-(\text{CH}_2)_n-\text{G}-(\text{CH}_2)_m-$   
 where n is 2, or 3;  
 m is 1, 2, or 3; and  
 25 G is methylene, 1,2 phenylene, oxygen, sulfur or  $\text{NR}_6$ ,

wherein  $R_6$  is lower alkyl, phenyl, 2-, 3-, or 4-pyridyl, 2- or 3-thienyl or 2-, 4- or 5-pyrimidinyl, or

$R_6$  is phenylalkyl, 2-, 3-, or 4-pyridylalkyl, 2- or 3-thienylalkyl, or 2-, 4- or 5-pyrimidinylalkyl, where each alkyl is lower alkyl; and

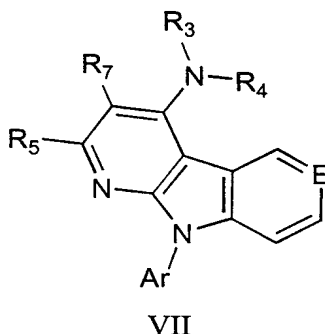
5  $R_5$  is hydrogen, halogen, lower alkyl, lower alkoxy, or thioalkoxy.

Preferred compounds of formula VI are those where at least one of  $R_a$ ,  $R_b$ , or  $R_c$  is present in one of the two ortho positions of the phenyl group to which they are attached. More preferred compounds of formula VI are those where at least two of  $R_a$ ,  $R_b$ , or  $R_c$  are present in one ortho position and the para position. Still more preferred compounds of  
10 formula VI are those where the  $R_a$ ,  $R_b$ , or  $R_c$  are present in both ortho positions and the para position, i.e., a 2, 4, 6-trisubstituted phenyl group. The preferred  $R_a$ ,  $R_b$ , or  $R_c$  are lower alkyl groups or halogen, particularly fluorine. More preferred aryl substituents are methyl groups.

Other preferred compounds of formula VI are those where the  $NR_3R_4$  group is a disubstituted amino group, e.g., dialkyl amino. A particularly preferred  $NR_3R_4$  group is  
15 dipropylamino. In preferred compounds of formula VI, E represents carbon.

In yet other preferred compounds of formula VI,  $R_7$  is hydrogen.

The invention further provides compounds of formula VII



20 wherein

E represents  $CH_2$  or  $NR_6$ , wherein  $R_6$  is hydrogen or lower alkyl;

Ar is phenyl, 2-, 3-, or 4-pyridyl, 2- or 3-thienyl, 4- or 5-pyrimidinyl, each of which is monosubstituted or optionally di- or trisubstituted with halogen, hydroxy,  
25 lower alkyl, or lower alkoxy, provided that at least one of the ortho positions of Ar is substituted;

$R_7$  is hydrogen or alkyl;

$R_3$  and  $R_4$  are not both hydrogen and independently represent

hydrogen, lower alkyl, phenyl, 2-, 3-, 4-pyridyl, 2- or 3-thienyl or 2-, 4-, or 5-pyrimidinyl, each of which is optionally mono- or disubstituted with halogen, hydroxy, lower alkyl, or lower alkoxy;

phenylalkyl, 2-, 3-, or 4-pyridylalkyl, 2- or 3-thienylalkyl, or 2-, 4-, or 5-pyrimidinylalkyl, where each alkyl is lower alkyl,

cycloalkyl having 3-8 carbon atoms, cycloalkyl lower alkyl, 2-hydroxyethyl or 3-hydroxypropyl, each of which is optionally mono or disubstituted with lower alkyl; or

$R_3$  and  $R_4$  taken together represent  $-(CH_2)_n-G-(CH_2)_m-$

where  $n$  is 2, or 3;

$m$  is 1, 2, or 3; and

$G$  is methylene, 1,2 phenylene, oxygen, sulfur or  $NR_6$ ,

wherein  $R_6$  is lower alkyl, phenyl, 2-, 3-, or 4-pyridyl, 2- or 3-thienyl or 2-, 4- or 5-pyrimidinyl, or

$R_6$  is phenylalkyl, 2-, 3-, or 4-pyridylalkyl, 2- or 3-thienylalkyl, or 2-, 4- or 5-pyrimidinylalkyl, where each alkyl is lower alkyl; and

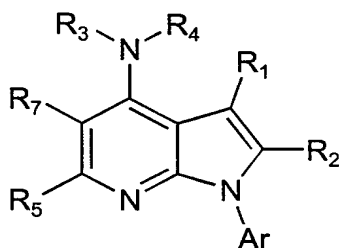
$R_5$  is hydrogen, halogen, lower alkyl, lower alkoxy, or thioalkoxy.

Preferred compounds of formula VII are those where  $Ar$  is a disubstituted aryl or heteroaryl group having substituents in one ortho position and the para position. More preferred compounds of formula VII are those where  $Ar$  is a trisubstituted aryl or heteroaryl group having substituents in both ortho positions and the para position, i.e., a 2, 4, 6-trisubstituted aryl group. The most preferred aryl group is phenyl. The preferred aryl substituents are lower alkyl groups or halogen, particularly fluorine. More preferred aryl substituents are methyl groups.

Other preferred compounds of formula VII are those where the  $NR_3R_4$  group is a disubstituted amino group, e.g., dialkyl amino. A particularly preferred  $NR_3R_4$  group is dipropylamino. In preferred compounds of formula VII,  $E$  represents carbon.

In still other preferred compounds of formula VII,  $R_7$  is hydrogen.

The invention also provides compounds of formula VIII:



VIII

wherein

R<sub>1</sub> is hydrogen or lower alkyl;

5 R<sub>2</sub> is hydrogen, halogen, lower alkyl, lower alkoxy, or thioalkoxy; or

Ar is phenyl, 2-, 3-, or 4-pyridyl, 2- or 3-thienyl, 4- or 5-pyrimidinyl, each of which is monosubstituted, or optionally di- or trisubstituted with halogen, hydroxy, lower alkyl, or lower alkoxy, provided that at least one of the ortho positions of Ar is substituted;

10 R<sub>7</sub> is hydrogen or alkyl;

R<sub>3</sub> and R<sub>4</sub> are not both hydrogen and independently represent

hydrogen, lower alkyl, phenyl, 2-, 3-, or 4-pyridyl, 2- or 3-thienyl or 2-, 4-, or 5-pyrimidinyl, each of which is optionally mono- or disubstituted with halogen, hydroxy, lower alkyl, or lower alkoxy,

15 phenylalkyl, 2-, 3-, or 4-pyridylalkyl, 2- or 3-thienylalkyl, or 2-, 4-, or 5-pyrimidinylalkyl, where each alkyl is lower alkyl,

cycloalkyl having 3-8 carbon atoms, cycloalkyl lower alkyl, 2-hydroxyethyl or 3-hydroxypropyl, each of which is optionally mono or disubstituted with lower alkyl; or

20 R<sub>3</sub> and R<sub>4</sub> taken together represent  $-(CH_2)_n-G-(CH_2)_m-$

where n is 2, or 3;

m is 1, 2, or 3; and

G is methylene, 1,2 phenylene, oxygen, sulfur or NR<sub>6</sub>,

wherein R<sub>6</sub> is lower alkyl, phenyl, 2-, 3-, or 4-pyridyl, 2- or 3-thienyl or 2-, 4- or 5-pyrimidinyl, or

25 R<sub>6</sub> is phenylalkyl, 2-, 3-, or 4-pyridylalkyl, 2- or 3-thienylalkyl, or 2-, 4- or 5-pyrimidinylalkyl where each alkyl is lower alkyl; and

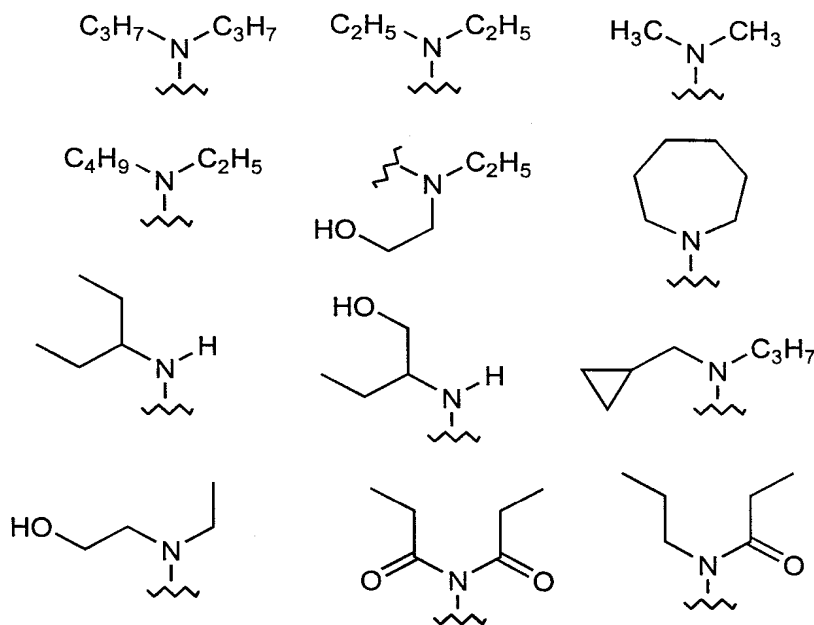
R<sub>5</sub> is hydrogen, halogen, lower alkyl, lower alkoxy, or thioalkoxy.

Preferred compounds of formula VIII are those where Ar is a disubstituted aryl or heteroaryl group having substituents in one ortho position and the para position. More preferred compounds of formula VIII are those where Ar is a trisubstituted aryl or heteroaryl group having substituents in both ortho positions and the para position, i.e., a 2, 4, 6-trisubstituted aryl group. The most preferred aryl group is phenyl. The preferred aryl substituents are lower alkyl groups or halogen, particularly fluorine. More preferred aryl substituents are methyl groups.

Other preferred compounds of formula VIII are those where the  $\text{NR}_3\text{R}_4$  group is a disubstituted amino group, e.g., dialkyl amino. A particularly preferred  $\text{NR}_3\text{R}_4$  group is dipropylamino.

In still other preferred compounds of formula VIII,  $\text{R}_1$  and  $\text{R}_2$  are independently alkyl groups. In more preferred compounds of formula VIII,  $\text{R}_1$  and  $\text{R}_2$  are both methyl.

In the compounds of the invention, preferred  $\text{NR}_3\text{R}_4$  groups include the following:



Representative compounds of the present invention, which are encompassed by Formula I, include, but are not limited to the compounds in Figure I and their pharmaceutically acceptable salts. Non-toxic pharmaceutically acceptable salts include salts of acids such as hydrochloric, phosphoric, hydrobromic, sulfuric, sulfinic, formic, toluene sulfonic, hydroiodic, acetic and the like. Those skilled in the art will recognize a wide variety of non-toxic pharmaceutically acceptable addition salts.



The present invention also encompasses the acylated prodrugs of the compounds of Formula I. Those skilled in the art will recognize various synthetic methodologies which may be employed to prepare non-toxic pharmaceutically acceptable addition salts and acylated prodrugs of the compounds encompassed by Formula I.

5 By aryl or "Ar" is meant an aromatic carbocyclic group having a single ring (e.g., phenyl), multiple rings (e.g., biphenyl), or multiple condensed rings in which at least one is aromatic, (e.g., 1,2,3,4-tetrahydronaphthyl, naphthyl, anthryl, or phenanthryl), which is optionally mono-, di-, or trisubstituted with, e.g., halogen, lower alkyl, lower alkoxy, lower alkylthio, trifluoromethyl, lower acyloxy, aryl, heteroaryl, and hydroxy.

10 By aryl or "Ar" is also meant heteroaryl groups where heteroaryl is defined as 5, 6, or 7 membered aromatic ring systems having at least one hetero atom selected from the group consisting of nitrogen, oxygen and sulfur. Examples of heteroaryl groups are pyridyl, pyrimidinyl, pyrrolyl, pyrazolyl, pyrazinyl, pyridazinyl, oxazolyl, furanyl, quinoliny, isoquinoliny, thiazolyl, and thienyl, which can optionally be substituted with, e.g., halogen,  
15 lower alkyl, lower alkoxy, lower alkylthio, trifluoromethyl, lower acyloxy, aryl, heteroaryl, and hydroxy.

By alkyl and lower alkyl is meant straight and branched chain alkyl groups having from 1-6 carbon atoms. Specific non-limiting examples of alkyl groups are methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert-butyl, sec-butyl, neopentyl and n-pentyl.

20 By lower alkoxy and alkoxy is meant straight and branched chain alkoxy groups having from 1-6 carbon atoms.

By thioalkoxy or alkylthio is meant a group of the formula -S-alkyl, where the alkyl is straight or branched chain alkyl having from 1-6 carbon atoms.

By halogen is meant fluorine, chlorine, bromine and iodine.

25 The pharmaceutical utility of compounds of this invention are indicated by the following assay for CRF receptor activity.

#### **Assay for CRF receptor binding activity**

30 CRF receptor binding was performed using a modified version of the assay described by Grigoriadis and De Souza (Biochemical, Pharmacological, and Autoradiographic Methods to Study Corticotropin-Releasing Factor Receptors. *Methods in Neurosciences*, Vol. 5, 1991). Membrane pellets containing CRF receptors were resuspended in 50mM Tris buffer pH 7.7 containing 10mM MgCl<sub>2</sub> and 2mM EGTA and centrifuged for 10 minutes at 48000g. Membranes were washed again and brought to a final concentration of 1500ug/ml in binding

buffer (Tris buffer above with .1 % BSA, .15mM bacitracin and .01 mg/ml aprotinin.). For the binding assay, 100ul of the membrane preparation was added to 96 well microtube plates containing 100ul of <sup>125</sup>I-CRF (SA 2200 Ci/mmol , final concentration of 100 pM) and 50 ul of drug. Binding was carried out at room temperature for 2 hours. Plates were then harvested on a Brandel 96 well cell harvester and filters were counted for gamma emissions on a Wallac 1205 Betaplate liquid scintillation counter. Non specific binding was defined by 1 uM cold CRF. IC<sub>50</sub> values were calculated with the non-linear curve fitting program RS/1 (BBN Software Products Corp., Cambridge, MA). The IC<sub>50</sub> for Compound 1 of this invention is 0.011 μM.

The compounds of general formula I may be administered orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition, there is provided a pharmaceutical formulation comprising a compound of general formula I and a pharmaceutically acceptable carrier. One or more compounds of general formula I may be present in association with one or more non-toxic pharmaceutically acceptable carriers and/or diluents and/or adjuvants and if desired other active ingredients. The pharmaceutical compositions containing compounds of general formula I may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs.

Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a

longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydropropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may

be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monoleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monoleate.

5 The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be  
10 formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride  
15 solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono-or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of general formula I may also be administered in the form of  
20 suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

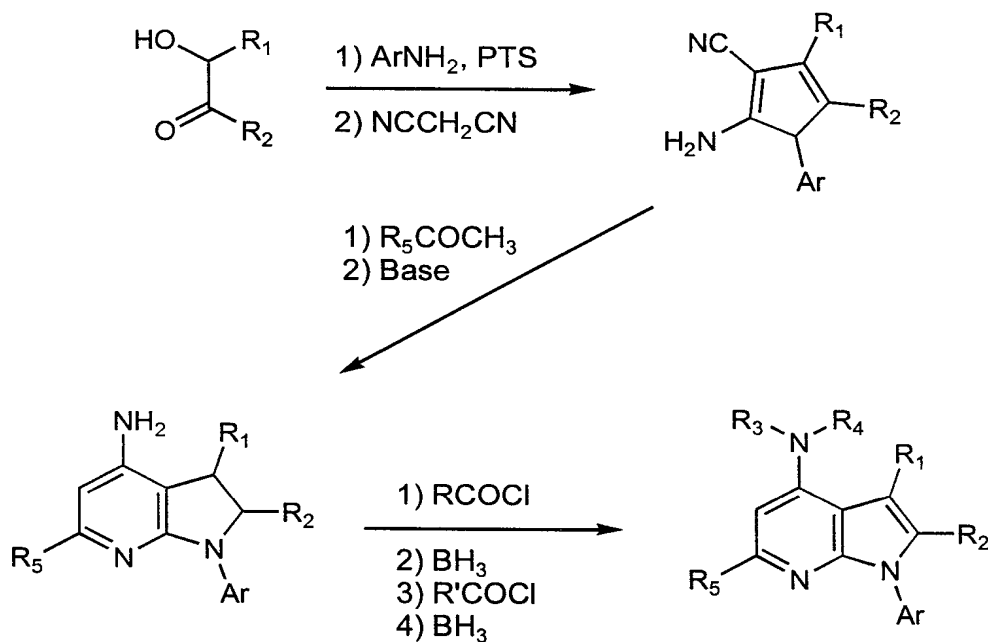
Compounds of general formula I may be administered parenterally in a sterile  
25 medium. The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anesthetics, preservatives and buffering agents can be dissolved in the vehicle.

Dosage levels of the order of from about 0.1 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (about 0.5 mg to  
30 about 7 g per patient per day). The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

A representative illustration of methods suitable for the preparation of compounds of the present invention is shown in Schemes I and II. Those having skill in the art will recognize that the starting materials may be varied and additional steps employed to produce compounds encompassed by the present invention.

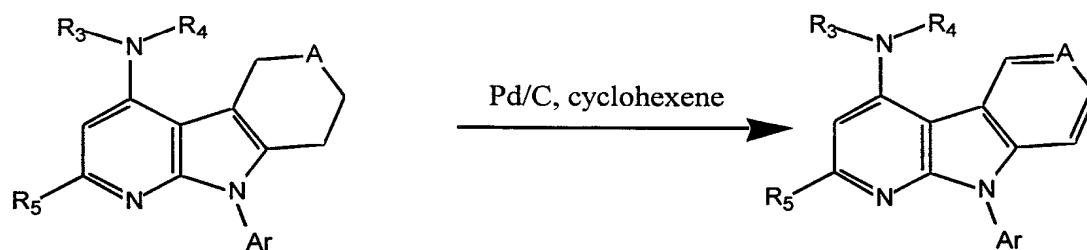
### Scheme I



wherein Ar, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, and R<sub>5</sub> are as defined above for formula I.

In the case where a desired compound of the invention that may be prepared according to Scheme I includes R<sub>7</sub> as alkyl, the intermediate 2-amino-1-aryl-3-cyanopyrrole is reacted with base and a compound of the formula R<sub>5</sub>COCH<sub>2</sub>R<sub>7</sub>, where R<sub>7</sub> is alkyl.

### Scheme II



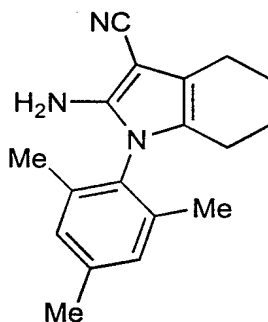
where A is NH or CH<sub>2</sub>, and Ar, R<sub>3</sub>, R<sub>4</sub>, and R<sub>5</sub> are as defined above for formula I...

- 5 As mentioned above, where a desired compound of the invention that may be prepared according to Scheme II includes R<sub>7</sub> as alkyl, the intermediate 2-amino-1-aryl-3-cyanopyrrole is reacted with base and a compound of the formula R<sub>5</sub>COCH<sub>2</sub>R<sub>7</sub>, where R<sub>7</sub> is alkyl.

The disclosure in this application of all articles and references, including patents, are incorporated herein by reference.

One skilled in the art will recognize that modifications may be made in the present invention without deviating from the spirit or scope of the invention. The invention is illustrated further by the following examples which are not to be construed as limiting the invention or scope of the specific procedures or compositions described herein.

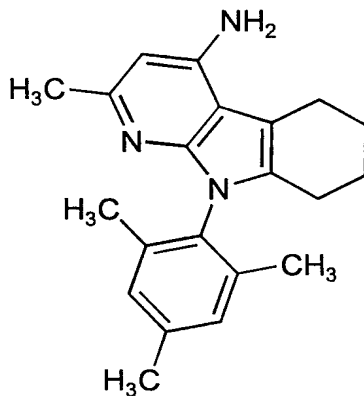
### Example IA



1a

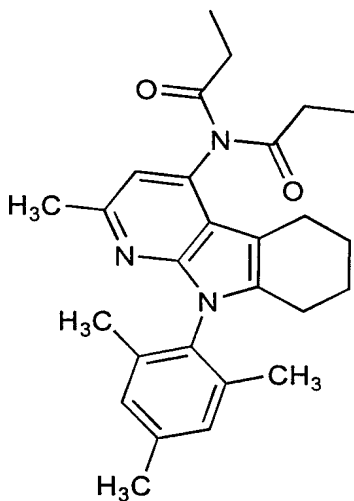
A mixture of 2,4,6-trimethylaniline (10.5 g 78 mmol), 2-hydroxycyclohexanone dimer (8.9 g, 39 mmol) and pTsOH (44 mg) was refluxed in 100 mL of toluene. Water was removed using a Dean-Stark apparatus. After 2 hours the solution was cooled and malononitrile (5.2 g) dissolved in 20 mL toluene was added. The mixture was refluxed for another 8 hours then the solvent was removed under reduced pressure. The crude product was triturated with ether and some ethanol, and collected by filtration as a tan solid to afford the aminonitrile 1a.

### Example IB



**1b**

The aminonitrile **1a** (1.1 g, 4.0 mmol) prepared above was stirred with anhydrous acetone (1.5 mL), pTsOH (10 mg) and 4A molecular sieves (1 g) in 10 mL benzene at 60°C for 10 hours. The mixture was then filtered through celite pretreated with triethylamine. The volatile solvents were removed under reduced pressure. The residual material was dissolved in 20 mL THF and treated with lithium diisopropylamide (2.0 M, 4 mL) under ice cooling. After 1 hour the mixture was poured into water and extracted with ethyl acetate. The organic layer was subsequently extracted with 5% hydrochloric acid. The aqueous layer was made alkaline with 10N sodium hydroxide and extracted with dichloromethane. The extract was washed with water then dried over sodium sulfate and concentrated to afford 2-Methyl-6,7,8,9-tetrahydro-9-(2,4,6-trimethylphenyl)-5H-pyrido[2,3-b]indol-4-amine **1b** as a white solid.

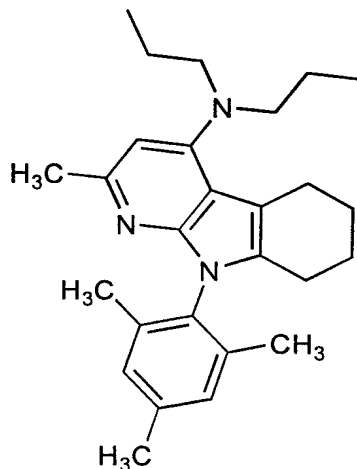
**Example IC****1c**

2-Methyl-6,7,8,9-tetrahydro-9-(2,4,6-trimethylphenyl)-5H-pyrido[2,3-b]indol-4-amine (**1b**) (470 mg) dissolved in 10 mL dichloroethane was refluxed for 3 hours with propionyl chloride (0.5 mL). The residual reagents were evaporated under reduced pressure. The crude product was partitioned between aqueous sodium carbonate solution and dichloromethane. The organic extract was dried over sodium sulfate and concentrated. The solid, diacylated product was triturated with hexanes and collected by filtration to afford N,N-Dipropionyl-2-



methyl-6,7,8,9-tetrahydro-9-(2,4,6-trimethyl phenyl)-5H-pyrido[2,3-b] indol-4-amine 1c as a white solid.

**Example ID**



Compound 1

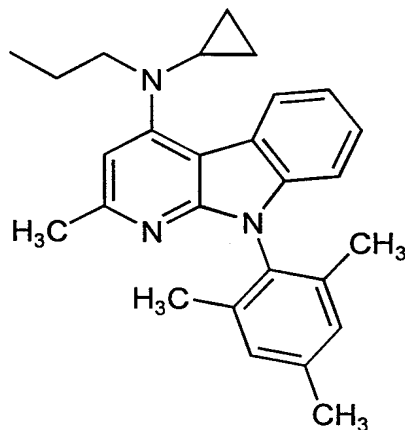
N,N-Dipropionyl-2-methyl-9-(2,4,6-trimethylphenyl)-5H-pyrido[2,3-b] indol-4-amine 1c (312 mg) was refluxed in 8 mL THF with borane-methylsulfide complex (10 M, 1.2 mL) for 10 hours. After cooling the solution it was carefully quenched with 5 mL of methanol. The resulting solution was refluxed for another 2 hours then concentrated. The dialkylamine product was purified on silica gel using 20% ethyl acetate in hexanes as eluant to afford N,N-Dipropyl-2-methyl-6,7,8,9-tetrahydro-9-(2,4,6-trimethylphenyl)-5H-pyrido[2,3-b]indol-4-amine (Compound 1) as a white solid, m.p.: 117-118°C.

**Example II**

The following compounds are prepared essentially according to the procedurse described in Examples IA-D:

a) N-Propyl-N-cyclopropylmethyl-2-methyl-6,7,8,9-tetrahydro-9-(2,4,6-trimethylphenyl)-5H-pyrido[2,3-b]indol-4-amine (Compound 2).

b) N-Propyl-N-cyclopropylmethyl-2-methyl-9-(2,4,6-trimethylphenyl)-9H-pyrido[2,3-b]indol-4-amine (Compound 3).



Compound 3

5

c) N-Butyl-N-Ethyl-2-methyl-6,7,8,9-tetrahydro-9-(2,4,6-trimethylphenyl)-5H-pyrido[2,3-b]indol-4-amine (Compound 4).

d) N,N-Dipropyl-2-methyl-9-(2,4,6-trimethylphenyl)-9H-pyrido[2,3-b]indol-4-amine (Compound 5).

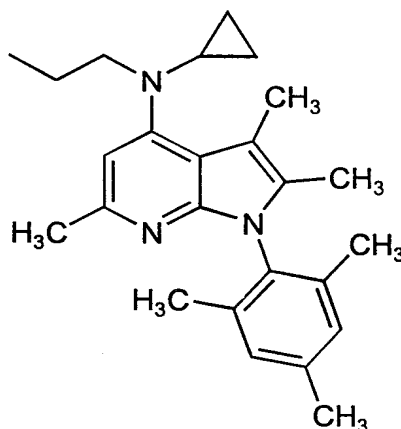
10

e) N-Butyl-N-Ethyl-2-methyl-9-(2,4,6-trimethylphenyl)-9H-pyrido[2,3-b]indol-4-amine (Compound 6).

15

f) N,N-Dipropyl-1-(2,4,6-trimethylphenyl)-2,3,6-trimethyl-1H-pyrrolo[2,3-b]pyridin-4-amine (Compound 7).

g) N-Cyclopropylmethyl-N-propyl-1-(2,4,6-trimethylphenyl)-2,3,6-trimethyl-1H-pyrrolo[2,3-b]pyridin-4-amine (Compound 8).



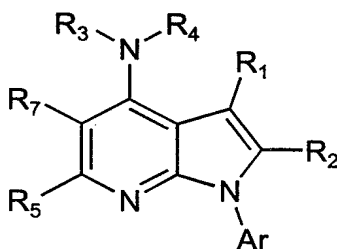
Compound 8

- h) N-Butyl-N-ethyl-1-(2,4,6-trimethylphenyl)-2,3,6-trimethyl-1H-pyrrolo[2,3-  
5 b]pyridin-4-amine (Compound 9).

10 The invention and the manner and process of making and using it, are now described in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, to make and use the same. It is to be understood that the foregoing describes preferred embodiments of the present invention and that modifications may be made therein without departing from the spirit or scope of the present invention as set forth in the claims. To particularly point out and distinctly claim the subject matter regarded as invention, the following claims conclude this specification.

**WHAT IS CLAIMED IS:**

- 5 1. A compound of the formula:



or the pharmaceutically acceptable salts thereof wherein

- 10 Ar is phenyl, 2-, 3-, or 4-pyridyl, 2-or 3-thienyl, 4-or 5-pyrimidinyl, each of which is monosubstituted, or optionally di- or trisubstituted with halogen, hydroxy, lower alkyl, or lower alkoxy, provided that at least one of the ortho positions of Ar is substituted;

R<sub>1</sub> is hydrogen or lower alkyl;

R<sub>7</sub> is hydrogen or alkyl;

- 15 R<sub>2</sub> is hydrogen, halogen, lower alkyl, lower alkoxy, or thioalkoxy; or

R<sub>1</sub> and R<sub>2</sub> taken together represent  $-(CH_2)_n-A-(CH_2)_m-$  where n is 2, 3 or 4, A is methylene, oxygen, sulfur or NR<sub>6</sub>, wherein R<sub>6</sub> is hydrogen or lower alkyl, and m is 0, 1 or 2; or

R<sub>1</sub> and R<sub>2</sub> taken together represent  $-CH=A=CH=CH-$ , where A is CH or N;

- 20 R<sub>3</sub> and R<sub>4</sub> are not both hydrogen and independently represent

hydrogen, lower alkyl, phenyl, 2-, 3-, or 4-pyridyl, 2-or 3-thienyl or 2-, 4-, or 5-pyrimidinyl, each of which is optionally mono- or disubstituted with halogen, hydroxy, lower alkyl, or lower alkoxy,

- 25 phenylalkyl, 2-, 3-, or 4-pyridylalkyl, 2-or 3-thienylalkyl, or 2-, 4-, or 5-pyrimidinylalkyl, where each alkyl is lower alkyl,

cycloalkyl having 3-8 carbon atoms, cycloalkyl lower alkyl, 2-hydroxyethyl or 3-hydroxypropyl, each of which is optionally mono or disubstituted with lower alkyl; or

R<sub>3</sub> and R<sub>4</sub> taken together represent  $-(CH_2)_n-G-(CH_2)_m-$

where n is 2, or 3;

m is 1, 2, or 3; and

G is methylene, 1,2 phenylene, oxygen, sulfur or NR<sub>6</sub>,

wherein R<sub>6</sub> is lower alkyl, phenyl, 2-, 3-, or 4-pyridyl, 2- or 3-thienyl

or 2-, 4- or 5-pyrimidinyl, or

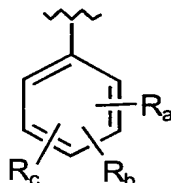
R<sub>6</sub> is phenylalkyl, 2-, 3-, or 4-pyridylalkyl, 2- or 3-thienylalkyl, or 2-,

4- or 5-pyrimidinylalkyl where each alkyl is lower alkyl; and

R<sub>5</sub> is hydrogen, halogen, lower alkyl, lower alkoxy, or thioalkoxy.

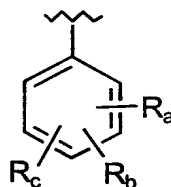
2. A compound according to Claim 2 wherein R<sub>1</sub> and R<sub>2</sub> taken together represent -(CH<sub>2</sub>)<sub>n</sub>-A-(CH<sub>2</sub>)<sub>m</sub>- where n is 2, 3 or 4, A is methylene, oxygen, sulfur or NMe, and m is 0, 1 or 2.

3. A compound according to Claim 2, wherein Ar is



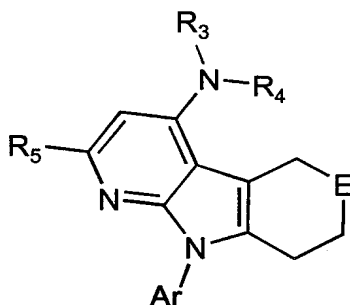
where R<sub>a</sub>, R<sub>b</sub>, and R<sub>c</sub> independently represent halogen, hydroxy, lower alkyl, or lower alkoxy.

4. A compound according to Claim 1, wherein Ar. is



where R<sub>a</sub>, R<sub>b</sub>, and R<sub>c</sub> independently represent halogen, hydroxy, lower alkyl, or lower alkoxy.

5. A compound of the formula:



or the pharmaceutically acceptable salts thereof wherein

E represents  $\text{CH}_2$  or  $\text{NR}_6$ , wherein  $\text{R}_6$  is hydrogen or lower alkyl;

Ar is phenyl, 2-, 3-, or 4-pyridyl, 2- or 3-thienyl, 4- or 5-pyrimidinyl, each of which is monosubstituted or optionally di- or trisubstituted with halogen, hydroxy, lower alkyl, or lower alkoxy, provided that at least one of the ortho positions of Ar is substituted;

$\text{R}_3$  and  $\text{R}_4$  are not both hydrogen and independently represent

hydrogen, lower alkyl, phenyl, 2-, 3-, 4-pyridyl, 2- or 3-thienyl or 2-, 4-, or 5-pyrimidinyl, each of which is optionally mono- or disubstituted with halogen, hydroxy, lower alkyl, or lower alkoxy;

phenylalkyl, 2-, 3-, or 4-pyridylalkyl, 2- or 3-thienylalkyl, or 2-, 4-, or 5-pyrimidinylalkyl, where each alkyl is lower alkyl,

cycloalkyl having 3-8 carbon atoms, cycloalkyl lower alkyl, 2-hydroxyethyl or 3-hydroxypropyl, each of which is optionally mono or disubstituted with lower alkyl; or

$\text{R}_3$  and  $\text{R}_4$  taken together represent  $-(\text{CH}_2)_n-\text{G}-(\text{CH}_2)_m-$

where n is 2, or 3;

m is 1, 2, or 3; and

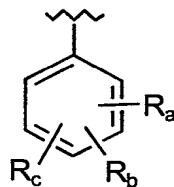
G is methylene, 1,2 phenylene, oxygen, sulfur or  $\text{NR}_6$ ,

wherein  $\text{R}_6$  is lower alkyl, phenyl, 2-, 3-, or 4-pyridyl, 2- or 3-thienyl or 2-, 4- or 5-pyrimidinyl, or

$\text{R}_6$  is phenylalkyl, 2-, 3-, or 4-pyridylalkyl, 2- or 3-thienylalkyl, or 2-, 4- or 5-pyrimidinylalkyl, where each alkyl is lower alkyl; and

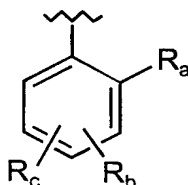
$\text{R}_5$  is hydrogen, halogen, lower alkyl, lower alkoxy, or thioalkoxy.

6. A compound according to Claim 5, wherein Ar is



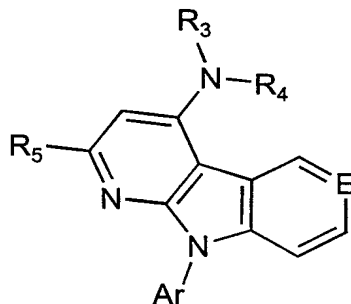
where  $R_a$ ,  $R_b$ , and  $R_c$  independently represent halogen, hydroxy, lower alkyl, or lower alkoxy.

- 5            7.        A compound according to Claim 2, wherein Ar is



where  $R_a$ ,  $R_b$ , and  $R_c$  independently represent halogen, hydroxy, lower alkyl, or lower alkoxy.

- 10           8.        A compound of the formula:



or the pharmaceutically acceptable salts thereof wherein

E represents  $\text{CH}_2$  or  $\text{NR}_6$ , wherein  $R_6$  is hydrogen or lower alkyl;

Ar is phenyl, 2-, 3-, or 4-pyridyl, 2- or 3-thienyl, 4- or 5-pyrimidinyl, each of which is monosubstituted or optionally di- or trisubstituted with halogen, hydroxy, lower alkyl, or lower alkoxy, provided that at least one of the ortho positions of Ar is substituted;

$R_3$  and  $R_4$  are not both hydrogen and independently represent

hydrogen, lower alkyl, phenyl, 2-, 3-, 4-pyridyl, 2- or 3-thienyl or 2-, 4-, or 5-pyrimidinyl, each of which is optionally mono- or disubstituted with halogen, hydroxy, lower alkyl, or lower alkoxy;

phenylalkyl, 2-, 3-, or 4-pyridylalkyl, 2- or 3-thienylalkyl, or 2-, 4-, or 5-pyrimidinylalkyl, where each alkyl is lower alkyl,  
 cycloalkyl having 3-8 carbon atoms, cycloalkyl lower alkyl, 2-hydroxyethyl or  
 3-hydroxypropyl, each of which is optionally mono or disubstituted  
 with lower alkyl; or

$R_3$  and  $R_4$  taken together represent  $-(CH_2)_n-G-(CH_2)_m-$

where  $n$  is 2, or 3;

$m$  is 1, 2, or 3; and

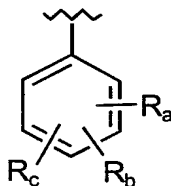
$G$  is methylene, 1,2 phenylene, oxygen, sulfur or  $NR_6$ ,

wherein  $R_6$  is lower alkyl, phenyl, 2-, 3-, or 4-pyridyl, 2- or 3-thienyl  
 or 2-, 4- or 5-pyrimidinyl, or

$R_6$  is phenylalkyl, 2-, 3-, or 4-pyridylalkyl, 2- or 3-thienylalkyl, or 2-,  
 4- or 5-pyrimidinylalkyl, where each alkyl is lower alkyl; and

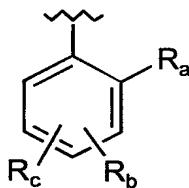
$R_5$  is hydrogen, halogen, lower alkyl, lower alkoxy, or thioalkoxy.

9. A compound according to Claim 8, wherein Ar is



where  $R_a$ ,  $R_b$ , and  $R_c$  independently represent halogen, hydroxy, lower alkyl, or lower alkoxy.

10. A compound according to Claim 8, wherein Ar is



where  $R_a$ ,  $R_b$ , and  $R_c$  independently represent halogen, hydroxy, lower alkyl, or lower alkoxy.

11. A compound according to Claim 2 wherein  $R_1$  and  $R_2$  taken together represent  $-CH=A-CH=C-$  where  $A$  is CH or N.



12. A compound according to Claim 1 which is N,N-Dipropyl-2-methyl-6,7,8,9-tetrahydro-9-(2,4,6-trimethylphenyl)-5H-pyrido[2,3-b]indol-4-amine.

5 13. A compound according to Claim 1 which is N-Propyl-N-cyclopropylmethyl-2-methyl-6,7,8,9-tetrahydro-9-(2,4,6-trimethylphenyl)-5H-pyrido[2,3-b]indol-4-amine.

14. A compound according to Claim 1 which is N-Propyl-N-cyclopropylmethyl-2-methyl-9-(2,4,6-trimethylphenyl)-9H-pyrido[2,3-b]indol-4-amine.

10 15. A compound according to Claim 1 which is N-Butyl-N-Ethyl-2-methyl-6,7,8,9-tetrahydro-9-(2,4,6-trimethylphenyl)-5H-pyrido[2,3-b]indol-4-amine.

16. A compound according to Claim 1 which is N,N-Dipropyl-2-methyl-9-(2,4,6-trimethylphenyl)-9H-pyrido[2,3-b]indol-4-amine.

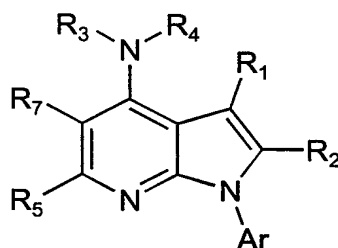
17. A compound according to Claim 1 which is N-Butyl-N-Ethyl-2-methyl-9-(2,4,6-trimethylphenyl)-9H-pyrido[2,3-b]indol-4-amine.

20 18. A compound according to Claim 1 which is N,N-Dipropyl-1-(2,4,6-trimethylphenyl)-2,3,6-trimethyl-1H-pyrrolo[2,3-b]pyridin-4-amine.

19. A compound according to Claim 1 which is N-Cyclopropylmethyl-N-propyl-1-(2,4,6-trimethylphenyl)-2,3,6-trimethyl-1H-pyrrolo[2,3-b]pyridin-4-amine.

25 20. A compound according to Claim 1 which is N-Butyl-N-ethyl-1-(2,4,6-trimethylphenyl)-2,3,6-trimethyl-1H-pyrrolo[2,3-b]pyridin-4-amine.

21. A compound of the formula:



or the pharmaceutically acceptable salts thereof wherein

R<sub>1</sub> is hydrogen or lower alkyl;

R<sub>2</sub> is hydrogen, halogen, lower alkyl, lower alkoxy, or thioalkoxy; or

5 Ar is phenyl, 2-, 3-, or 4-pyridyl, 2- or 3-thienyl, 4- or 5-pyrimidinyl, each of which is monosubstituted, or optionally di- or trisubstituted with halogen, hydroxy, lower alkyl, or lower alkoxy, provided that at least one of the ortho positions of Ar is substituted;

R<sub>7</sub> is hydrogen or alkyl;

10 R<sub>3</sub> and R<sub>4</sub> are not both hydrogen and independently represent

hydrogen, lower alkyl, phenyl, 2-, 3-, or 4-pyridyl, 2- or 3-thienyl or 2-, 4-, or 5-pyrimidinyl, each of which is optionally mono- or disubstituted with halogen, hydroxy, lower alkyl, or lower alkoxy,

15 phenylalkyl, 2-, 3-, or 4-pyridylalkyl, 2- or 3-thienylalkyl, or 2-, 4-, or 5-pyrimidinylalkyl, where each alkyl is lower alkyl, cycloalkyl having 3-8 carbon atoms, cycloalkyl lower alkyl, 2-hydroxyethyl or 3-hydroxypropyl, each of which is optionally mono or disubstituted with lower alkyl; or

R<sub>3</sub> and R<sub>4</sub> taken together represent  $-(CH_2)_n-G-(CH_2)_m-$

20 where n is 2, or 3;

m is 1, 2, or 3; and

G is methylene, 1,2 phenylene, oxygen, sulfur or NR<sub>6</sub>,

wherein R<sub>6</sub> is lower alkyl, phenyl, 2-, 3-, or 4-pyridyl, 2- or 3-thienyl or 2-, 4- or 5-pyrimidinyl, or

25 R<sub>6</sub> is phenylalkyl, 2-, 3-, or 4-pyridylalkyl, 2- or 3-thienylalkyl, or 2-, 4- or 5-pyrimidinylalkyl where each alkyl is lower alkyl; and

R<sub>5</sub> is hydrogen, halogen, lower alkyl, lower alkoxy, or thioalkoxy.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/05979

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D471/04 A61K31/44 //(C07D471/04,221:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 061 056 A (TROPONWERKE GMBH) 29 September 1982 see formula I and examples 2-5, page 16, and page 13, lines 7-20 ---	1-21
Y	WO 95 33750 A (PFIZER INC) 14 December 1995 see formula II, and definitions of R5 and B, and page 7 line 14-page 9, line 4 ---	1-21
Y	WO 94 13676 A (PFIZER INC) 23 June 1994 cited in the application see the whole document, especially definitions of B and R5 and examples --- -/--	1-21



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

### \* Special categories of cited documents :

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- "O" document referring to an oral disclosure, use, exhibition or other means
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- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

11 December 1997

Date of mailing of the international search report

23. 12. 97

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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/05979

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ZIMMERMANN W ET AL: "Pyrrolo[2,3-b]pyridines" ARCH. PHARM. (WEINHEIM, GER.) (ARPMAS);76; VOL.309 (7); PP.597-600, UNIV. BONN;PHARM. INST.; BONN; GER., XP002049850 see formulae 5 and 6 ---	1-21
A	WO 96 35689 A (NERUOGEN CORPORATION) 14 November 1996 see general formula -----	1-21

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. Application No

PCT/US 97/05979

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 61056 A	29-09-82	DE 3111155 A JP 57159784 A	30-09-82 01-10-82
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WO 9533750 A	14-12-95	AU 2453095 A BR 9502708 A EP 0764166 A FI 964894 A HU 75774 A JP 9507249 T NO 965237 A PL 320631 A	04-01-96 30-04-96 26-03-97 05-12-96 28-05-97 22-07-97 06-02-97 13-10-97
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WO 9413676 A	23-06-94	AU 5666494 A CA 2150016 A CN 1097758 A CZ 9501584 A EP 0674641 A FI 935585 A HU 70505 A JP 7509726 T NO 952398 A NZ 258690 A PL 309357 A ZA 9309271 A	04-07-94 23-06-94 25-01-95 17-01-96 04-10-95 18-06-94 30-10-95 26-10-95 16-06-95 29-01-97 02-10-95 12-06-95
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WO 9635689 A	14-11-96	US 5644057 A AU 5679096 A CA 2194756 A EP 0770080 A	01-07-97 29-11-96 14-11-96 02-05-97
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